NDA 76187

Levothyroxine Sodium
Tablets USP

0.025mg, 0.05mg, 0.075mg,
0.088mg, 0.1mg, 0.122mg,
0.125mg, 0.15mg, 0.175mg,
0.2mg and 0.3mg

Mylan Pharmaceuticals

Approval Date: June 5, 2002

Patent / Exclusivity

Search results from the "Rx" table for query on "021210."

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	UNITHROID
Applicant:	STEVENS J
Strength:	0.025MG
Application Number:	021210
Product Number:	001
Approval Date:	Aug 21, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	UNITHROID
Applicant:	STEVENS J
Strength:	0.05MG
Application Number:	021210
Product Number:	002
Approval Date:	Aug 21, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	UNITHROID
Applicant:	STEVENS J
Strength:	0.075MG
Application Number:	021210
Product Number:	003
Approval Date:	Aug 21, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM

Dosage Form;Route:	Tablet; Oral
Proprietary Name:	UNITHROID
Applicant:	STEVENS J
Strength:	0.088MG
Application Number:	021210
Product Number:	004
Approval Date:	Aug 21, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	UNITHROID
Applicant:	STEVENS J
Strength:	0.1MG
Application Number:	021210
Product Number:	005
Approval Date:	Aug 21, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	UNITHROID
Applicant:	STEVENS J
Strength:	0.112MG
Application Number:	021210
Product Number:	006
Approval Date:	Aug 21, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	UNITHROID
Applicant:	STEVENS J

Strength:	0.125MG
Application Number:	021210
Product Number:	007
Approval Date:	Aug 21, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	UNITHROID
Applicant:	STEVENS J
Strength:	0.15MG
Application Number:	021210
Product Number:	008
Approval Date:	Aug 21, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	UNITHROID
Applicant:	STEVENS J
Strength:	0.175MG
Application Number:	021210
Product Number:	009
Approval Date:	Aug 21, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	

Patent and Exclusivity Info for this product: Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	UNITHROID
Applicant:	STEVENS J
Strength:	0.2MG
Application Number:	021210
Product Number:	010

Approval Date:	Aug 21, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name:	UNITHROID
Applicant:	STEVENS J
Strength:	0.3MG
Application Number:	021210
Product Number:	011
Approval Date:	Aug 21, 2000
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	Click Here

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Active Ingredient Search Results from "Rx" table for query on "levothyroxine."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
021210		No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.025MG	UNITHROID	STEVENS J
021210		No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.05MG	UNITHROID	STEVENS J
021210		No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.075MG	UNITHROID	STEVENS J
021210		No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.088MG	UNITHROID	STEVENS J
021210		No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.112MG	UNITHROID	STEVENS J
021210		No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.125MG	UNITHROID	STEVENS J
021210		No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.15MG	UNITHROID	STEVENS J
021210		No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.175MG	UNITHROID	STEVENS J
021210		No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.1MG	UNITHROID	STEVENS J
021210		No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.2MG	UNITHROID	STEVENS J
021210		Yes	LEVOTHYROXINE SODIUM	Tablet; Oral	0.3MG	UNITHROID	STEVENS J

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Patent and Exclusivity Search Results from query on 021210 011.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

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Patent and Exclusivity Terms

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Patent and Exclusivity Search Results from query on 021210 001.

Patent Data

There are no unexpired patents for this product in the Orange Book Database.

[Note: Title I of the 1984 Amendments does not apply to drug products submitted or approved under the former Section 507 of the Federal Food, Drug and Cosmetic Act (antibiotic products). Drug products of this category will not have patents listed.]

Exclusivity Data

There is no unexpired exclusivity for this product.

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

Search results from the "Rx" table for query on "021210."

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name	UNITHROID
Applicant:	STEVENS J
Strength:	0.025MG
Application Number:	021210
Product Number:	001
Approval Date:	AUG 21, 2000
Reference Listed Drug:	No
RX/OTC/DISCN:	RX
TE Code:	**BX**
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name	UNITHROID
Applicant:	STEVENS J
Strength:	0.05MG
Application Number:	021210
Product Number:	002
Approval Date:	AUG 21, 2000
Reference Listed Drug:	No
RX/OTC/DISCN:	RX
TE Code:	**BX**
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name	UNITHROID
Applicant:	STEVENS J
Strength:	0.075MG
Application Number:	021210
Product Number:	003
Approval Date:	AUG 21, 2000
Reference Listed Drug:	No
RX/OTC/DISCN:	RX
TE Code:	**BX**
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM

Dosage Form;Route:	Tablet; Oral
Proprietary Name	UNITHROID
Applicant:	STEVENS J
Strength:	0.088MG
Application Number:	021210
Product Number:	004
Approval Date:	AUG 21, 2000
Reference Listed Drug:	No
RX/OTC/DISCN:	RX
TE Code:	BX
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name	UNITHROID
Applicant:	STEVENS J
Strength:	0.1MG
Application Number:	021210
Product Number:	005
Approval Date:	AUG 21, 2000
Reference Listed Drug:	No
RX/OTC/DISCN:	RX
TE Code:	BX
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name	UNITHROID
Applicant:	STEVENS J
Strength:	0.112MG
Application Number:	021210
Product Number:	006
Approval Date:	AUG 21, 2000
Reference Listed Drug:	No
RX/OTC/DISCN:	RX
TE Code:	BX
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name	UNITHROID
Applicant:	STEVENS J

Strength:	0.125MG
Application Number:	021210
Product Number:	007
Approval Date:	AUG 21, 2000
Reference Listed Drug:	No
RX/OTC/DISCN:	RX
TE Code:	**BX**
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name	UNITHROID
Applicant:	STEVENS J
Strength:	0.15MG
Application Number:	021210
Product Number:	008
Approval Date:	AUG 21, 2000
Reference Listed Drug:	No
RX/OTC/DISCN:	RX
TE Code:	**BX**
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name	UNITHROID
Applicant:	STEVENS J
Strength:	0.175MG
Application Number:	021210
Product Number:	009
Approval Date:	AUG 21, 2000
Reference Listed Drug:	No
RX/OTC/DISCN:	RX
TE Code:	**BX**
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name	UNITHROID
Applicant:	STEVENS J
Strength:	0.2MG
Application Number:	021210
Product Number:	010

Approval Date:	AUG 21, 2000
Reference Listed Drug:	No
RX/OTC/DISCN:	RX
TE Code:	BX
Patent and Exclusivity Info for this product:	Click Here

Active Ingredient:	LEVOTHYROXINE SODIUM
Dosage Form;Route:	Tablet; Oral
Proprietary Name	UNITHROID
Applicant:	STEVENS J
Strength:	0.3MG
Application Number:	021210
Product Number:	011
Approval Date:	AUG 21, 2000
Reference Listed Drug:	Yes
RX/OTC/DISCN:	RX
TE Code:	BX
Patent and Exclusivity Info for this product:	Click Here

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Proprietary Name Search Results from "Rx" table for query on "unithroid."

Appl No	TE Code	RLD	Active Ingredient	Dosage Form; Route	Strength	Proprietary Name	Applicant
021210	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.025MG	UNITHROID	STEVENS J
021210	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.05MG	UNITHROID	STEVENS J
021210	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.075MG	UNITHROID	STEVENS J
021210	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.088MG	UNITHROID	STEVENS J
021210	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.112MG	UNITHROID	STEVENS J
021210	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.125MG	UNITHROID	STEVENS J
021210	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.15MG	UNITHROID	STEVENS J
021210	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.175MG	UNITHROID	STEVENS J
021210	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.1MG	UNITHROID	STEVENS J
021210	BX	No	LEVOTHYROXINE SODIUM	Tablet; Oral	0.2MG	UNITHROID	STEVENS J
021210	BX	Yes	LEVOTHYROXINE SODIUM	Tablet; Oral	0.3MG	UNITHROID	STEVENS J

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NDA 76187

Levothyroxine Sodium
Tablets USP

0.025mg, 0.05mg, 0.075mg,
0.088mg, 0.1mg, 0.122mg,
0.125mg, 0.15mg, 0.175mg,
0.2mg and 0.3mg

Mylan Pharmaceuticals

Approval Date: June 5, 2002

Div Docket Memos

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 5, 2002

FROM: Gary Buehler 6/5/02
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: Approval of ANDA 76-187
Levothyroxine Sodium Tablets
Mylan Pharmaceuticals, Inc.

TO: Docket # 02P-0135/PSA1
ANDA 76-187 File

Jerome Stevens Pharmaceuticals Inc. (Jerome) submitted a Petition for a Stay of Action, No. 02P-0135/PSA1, dated March 26, 2002, and filed by the Agency on March 28, 2002. The petition requests that FDA immediately and indefinitely stay (1) all grants of drug pre-market authority that were based on New Drug Applications (NDAs) or Abbreviated New Drug Applications (ANDAs) that used, relied on, or were based on Jerome's confidential and trade secret manufacturing information for orally-administered levothyroxine sodium (LS) and (2) all pending and prospective NDAs and ANDAs that use, rely on, or are based on Jerome's confidential and trade secret manufacturing information for orally-administered LS. Jerome claimed in a Notice of Claims Pursuant to the Federal Tort Claims Act dated March 26, 2002 (Notice) that certain information that had been posted on the FDA's website (http://www.fda.gov/cder/) on August 22, 2000, regarding Jerome's NDA 21-210 for LS was confidential and trade secret information.

The Office of Generic Drugs has reviewed Mylan Pharmaceuticals, Inc. (Mylan)'s ANDA 76-187, submitted on June 5, 2001, and has determined that the Mylan ANDA did not use or rely on, and was not based on Jerome's allegedly confidential information. This determination is based on the fact that the batches Mylan used to support its ANDA were manufactured prior to the posting on the agency's website of the approval materials from Jerome's NDA for LS.[1]

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1 The filing of this memorandum solely represents a determination that the Mylan ANDA did not use or rely on, and was not based on Jerome's allegedly confidential information. It does not represent a determination with regard to any other issue, nor does it constitute an admission of any issue raised by Jerome's Petition or Notice.

ANDA 76-187
Mylan Pharmaceuticals, Inc.
Levothyroxine Sodium Tablets

cc: ANDA 76-187
Docket# 02P-0135/PSA1
Division File
C. Parise, HFD-600
D. Katz, GCF-1
K. Schifter, GCF-1
L. Whipkey GCF1
v:\firmsam\mylan\76187mem2fin.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Rockville, MD 20857

DATE: June 5, 2002

FROM: Lawrence X. Yu, Ph. D.
Deputy Director for Science (Actg.) Lawrence Yu
Office of Generic Drugs
Center for Drug Evaluation and Research June 5, 2002

SUBJECT: Approval of ANDA 76-187
Mylan Pharmaceuticals Inc
Levothyroxine Sodium Tablets

TO: The ANDA file for ANDA 76-187

Background

The Division of Bioequivalence, Office of Generic Drugs (OGD) has concluded that the Mylan ANDA 76-187, levothyroxine sodium tablets, meets the FDA's current bioequivalence criteria for AUC and Cmax (90% confidence interval with the limits of 80-125 based on log transformed data). The bioequivalence criteria are calculated using data that is not baseline corrected based upon current agency policy regarding this specific drug product. This policy is outlined in the Guidance to Industry *Guidance for Industry, Levothyroxine Sodium Tablets - In Vivo Pharmacokinetic and Bioavailability Studies and In Vitro Dissolution Testing* issued December 2000. The bioequivalence study submitted in Mylan's ANDA was found to be acceptable on December 31, 2001.

On May 08, 2002, Abbott Laboratories (Abbott) wrote to the FDA to request a meeting, and contended that bioavailability parameters calculated from baseline uncorrected data is much less sensitive to changes in bioavailability than is the case for bioequivalence assessment of nonendogenous compounds for which baseline data are essentially zero. Abbott contends that baseline correction should be considered for levothyroxine sodium drug products. Abbott proposed two alternative baseline correction methods on calculation of pharmacokinetic parameters[1]. The FDA's current policy for levothyroxine sodium drug products is to not correct baseline in the bioequivalence determination.

[1] A third method was also mentioned in this letter, but Abbott has not completed the necessary studies for this method at this time. FDA has indicated a willingness to meet with Abbott to discuss this subject once the final study report for the ongoing study is available.

Although these two alternative methods set forth by Abbott are not validated or accepted regulatory methods, OGD applied them to Mylan ANDA 76-187 to address the issues raised by Abbott

Methods

Pharmacokinetic/Statistical Analysis of Abbott's Proposed Methods

STATISTICAL ANALYSIS:

AUC(0-48hrs), Cmax and log transformed AUC(0-48hrs), and Cmax were analyzed by Analysis of Variance (ANOVA) with effects for treatments, sequence of dosing, subjects within sequence, and study period in the statistical model.

The two one-sided hypotheses at the α=0.05 level of significance were tested for AUC(0-48hrs) and Cmax in original scale and after log transformation, by constructing the 90% confidence intervals for the differences between the test and the reference least squares means, and were reported relative to the reference means.

These AUC(0-48hrs) and Cmax values were subjected to two baseline correction methods proposed by Abbott.

Method 1- This method assumes that the contribution of endogenous levothyroxine to the observed levothyroxine concentration is constant. The average of the –0.5, -0.25 and 0 time concentration values prior to dosing ($C_{baseline}$) are taken as representative endogenous levothyroxine concentrations over the next 48 hrs. Baseline corrected Cmax and AUC (0-48hrs) were calculated by:

Corrected Cmax = Observed Cmax-$C_{baseline}$

Endogenous AUC (0-48 hrs) = $C_{baseline} \times 48$ hrs

Corrected AUC (0-48 hrs) = Observed AUC (0-48 hrs) – Endogenous AUC (0-48 hrs)

Method 2- This method assumes that large doses of levothyroxine completely suppress levothyroxine production at the time of dosing. Consequently, the concentration of endogenous material declines exponentially from the baseline level, with a half-life of 7 days (168 hrs) that corresponds to a value for β of log2/168. Baseline corrected Cmax and AUC (0-48hrs) were calculated by:

Corrected Cmax = Observed Cmax- $C_{baseline} \exp(-\beta \times$ Observed Tmax)

Endogenous AUC (0-48hrs) = $C_{baseline}/\beta\ (1-\exp(-48 \times \beta))$

Corrected AUC (0-48hrs) = Observed AUC (0-48hrs) - Endogenous AUC (0-48hrs)

All calculations were done using SAS (The code is available upon request).

Results

Table 1. Mean pharmacokinetic parameters (± sd) for the 600 mcg dose of levothyroxine ANDA# 76187.

Parameter	Test	Reference	Ratio(T/R)[1]	90% CI
Ln AUC(0-48hrs), No baseline correction	8.64(0.12)	8.66(0.13)	0.98	96-100
Ln AUC(0-48hrs), Baseline correction, Method 1	7.40(0.24)	7.48(0.22)	0.92	85-99
Ln AUC(0-48hrs), Baseline correction, Method 2	7.61(0.19)	7.67(0.19)	0.94	88-99
Ln Cmax, No baseline correction	5.03(0.14)	5.06(0.14)	0.96	94-100
Ln Cmax, Baseline correction, Method 1	4.23(0.25)	4.32(0.21)	0.91	86-97
Ln Cmax, Baseline correction, Method 2	4.25(0.24)	4.33(0.21)	0.91	87-97

1.Ratio of Least Squares Geometric Means

Table 2. Mean pharmacokinetic parameters (± sd) for the 500 mcg dose of Levothyroxine ANDA# 76187.

Parameter	Test	Reference	Ratio(T/R)[1]	90% CI
Ln AUC(0-48hrs), No baseline correction	8.61(0.12)	8.61(0.11)	0.99	97-101
Ln AUC(0-48hrs), Baseline correction, Method 1	7.29(0.25)	7.33(0.26)	0.94	90-99
Ln AUC(0-48hrs), Baseline correction, Method 2	7.52(0.20)	7.55(0.21)	0.96	92-99
Ln Cmax, No baseline correction	4.95(0.13)	4.98(0.12)	0.95	93-99
Ln Cmax, Baseline correction, Method 1	4.04(0.25)	4.14(0.21)	0.88	83-94
Ln Cmax, Baseline correction, Method 2	4.06(0.24)	4.16(0.20)	0.88	84-94

1.Ratio of Least Squares Geometric Means

Table 3 Mean pharmacokinetic parameters (± sd) for the 300 mcg dose of Levothyroxine ANDA# 76187.

Parameter	Test	Reference	Ratio(T/R)[1]	90% CI
Ln AUC(0-48hrs), No baseline correction	8.68(0.10)	8.70(0.10)	0.99	97-100
Ln AUC(0-48hrs), Baseline correction, Method 1	7.55(0.22)	7.58(0.18)	0.96	90-102
Ln AUC(0-48hrs), Baseline correction, Method 2	7.73(0.17)	7.76(0.15)	0.97	92-102
Ln Cmax, No baseline correction	5.06(0.10)	5.10(0.09)	0.96	94-98
Ln Cmax, Baseline correction, Method 1	4.31(0.18)	4.37(0.18)	0.94	90-97
Ln Cmax, Baseline correction, Method 2	4.33(0.17)	4.38(0.18)	0.94	90-97

1.Ratio of Least Squares Geometric Means

Conclusion:

FDA has determined that although these two alternative methods are not validated or accepted regulatory methods, the Mylan levothyroxine sodium tablets meet the 90% confidence interval limit of 80-125, for AUC and Cmax when the baseline is adjusted according to the methods proposed by Abbott. This does not mean that the FDA has in any manner endorsed these two methods proposed by Abbott.

In fact, the current bioequivalence criteria for an ANDA for levothyroxine sodium tablets does not utilize baseline corrected data. Mylan's application meets FDA's current bioequivalence criteria.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Emord & Associates, P.C.
Burke Professional Center
5282 LynGate Court
Burke, VA 22015

JUN 5 2002

Reference Number: OGD 02-245

Dear Mr. Emord:

This letter is in response to your correspondence dated May 2, 2002. You state that you represent Jerome Stevens Pharmaceuticals Inc. (JSP). JSP is the holder of an approved new drug application (NDA) for levothyroxine sodium tablets (Unithroid™) and this drug product has been designated the reference listed drug in Approved Drug Products with Therapeutic Equivalence Evaluations (*Orange Book*). You request that the Office of Generic Drugs (OGD) confirm that any sponsor of an abbreviated new drug application (ANDA) seeking bioequivalence status to Unithroid™ will have to meet the specific criteria stated in your letter. You also stated that ANDAs must complete "the clinical requirements" before approval.

The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. No. 98-417) (the Hatch-Waxman Amendments) created section 505(j) of the Food, Drug, and Cosmetic Act (the Act), which established the current ANDA approval process.

Sections 505(j)(2)(A)(ii), (iii), and (iv) of the Act specify that an ANDA must contain information to show that the active ingredient, route of administration, dosage form and strength are the same as the listed drug and that the drug is bioequivalent to the listed drug. Under the Hatch-Waxman Amendments, the agency issued regulations that govern bioequivalence determinations. The regulations at 21 CFR 320.23(b) state that "Two products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions. . . ."

The Act does not require an ANDA to contain the same information as an NDA. (See section 505(b)(1) and (d) of the Act for the requirements for an NDA and 21 CFR 314.50 for more detailed regulatory requirements for the content and format of an NDA. See 505(j)(2) and (4) of the Act for the requirements for an ANDA application and 21 CFR 314.94 for more detailed regulatory requirements for the content and format of an ANDA.) Accordingly, ANDAs for levothyroxine sodium are not required to meet the same clinical study requirements as NDAs for levothyroxine sodium.

You raise three specific criteria regarding stability that you believe an ANDA must meet before the product can be considered to be bioequivalent to Unithroid™ and/or before a product may "be considered for substitution to Unithroid™." The application of these criteria to ANDAs is addressed more fully below, but FDA notes that stability and batch data are intended to demonstrate that a sponsor is able to successfully manufacture a product and that the product will be stable through the expiration date. A determination of bioequivalence is dictated by whether the rate and extent of the absorption of the ANDA product shows a significant difference from the reference listed product. (See 21 CFR 320.23(b)). Therapeutic equivalence refers to products that are bioequivalent and pharmaceutically equivalent. Drug products are considered pharmaceutical equivalents if they contain the same active ingredient, are of the same dosage form, route of administration, and are identical in strength or concentration. (See the Preface to the 21st edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).) Accordingly, while ANDAs must demonstrate adequate stability and batch data, these data do not determine bioequivalence or therapeutic equivalence.

The specific criteria you raised in your letter and OGD's comments follow:

1. "Successful completion of ICH stability guidelines at storage conditions of 6 months at 40° C and 75% RH and Long Term conditions of 25° C and 60 % RH. Conditions other than these cannot qualify a drug as a generic equivalent to Unithroid™."

   Under 21 CFR 314.94(a)(9), ANDA applicants are required to submit information on chemistry, manufacturing, and controls for the proposed drug product. This information includes stability data with proposed expiration data. (21 CFR 314.94(a)(9) imposes the requirements of 21 CFR 314.50(d)(1)(ii)(a) on ANDA applicants). However, ANDA applicants are not required to submit the same stability information to satisfy this requirement as NDA applicants because the stability data requirements for ANDAs are determined in part by the existence of a significant body of information for the dosage form and the existence of an approved application for the particular dosage form.

   To satisfy the stability requirements for an ANDA, ANDA applicants ordinarily submit 3 months of accelerated stability data at 40° C and 75% RH with testing at , 0 1, 2, and 3 months and/or full room temperature data in the initial submission of theANDA. . If acceptable, these data qualify an applicant for a tentative two-year expiration date. An ANDA applicant must confirm this dating by the submission of room temperature data and may obtain a longer expiration date if it provides long term stability data. OGD accepts either the ICH criteria of 25° C and 60 % RH or data generated at 25-30° C and ambient humidity. For information with respect to stability recommendations for an ANDA, please refer to the attached letters to industry dated November 8, 1991, and August 18, 1995 , which constitute guidance for industry developed and issued prior to the Good Guidance Practices published in February, 1997.

2. "No fewer than 3 batches of the high and low strengths and 2 batches of each other strength must meet the aforementioned criteria. This will insure the reproducibility of the product while maintaining the highest product quality."

For the reasons stated above, ANDA applicants are not required to submit the same batch information as NDAs. To satisfy the stability requirements for an ANDA, ANDA applicants ordinarily submit information from one batch of each strength for which it is seeking approval with a minimum of 100,000 tablets per batch. See the Office of Generic Drugs, Policy and Procedure Guide: # 22-90 – Revised September 13, 1990 (attached).

3. "Finally the use of Stability Overages ("spiking") must be prohibited. Manufacturers must formulate products to have potencies of NMT 100% at the time of release."

As indicated in the Guidance for Industry entitled Levothyroxine Sodium Products Enforcement of August 14, 2001 Compliance Date and Submission of New Applications, the FDA agrees that stability overages should be prohibited. Manufacturers should formulate their product to be targeted for release at not more than 100% of the labeled claim. The lots released for the drug product should have a normal distribution around 100% of the labeled claim.

If you have any questions, please call Ms. Cecelia Parise, R.Ph., Regulatory Policy Advisor to the Director, Office of Generic Drugs, at (301) 827-5845. In future correspondence regarding this issue, please include a copy of this letter and please style your submission in the form of a citizen petition as set forth in 21 CFR 10.30.

Sincerely yours,

Gary J. Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosures: Letters to industry dated November 8, 1991, and August 18, 1995; Office of Generic Drugs, Policy and Procedure Guide: # 22-90 – Revised September 13, 1990

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 29-Dec-2000 01:51pm EST
From: Donald Hare
HARE
Dept: HFD-604 MPN2 286
Tel No: 301-827-5845 FAX 301-594-0183

TO: Gary Buehler (BUEHLER)

CC: Robert West (WESTR)
CC: William Rickman (RICKMAN)
CC: Gregory Davis (DAVISG)
CC: Cecelia Parise (PARISEC)
CC: Dale Conner (CONNERD)
CC: Lizzie Sanchez (SANCHEZL)
CC: Rita Hassall (HASSALLR)

Subject: RE: levothyroxine

Gary:

I agree with your concern regarding the formulation of the JS levothyroxin (LT) tablets that were approved and the formulation of the JS LT tablets that were b[illegible] marketed without an approved application possibly not being the same. Although the formulation of the two LT tablets are probably the same I think that it will have to be checked out.

A similar situation occurred when a firm did a verapamil ER tablet BE study and used Searle's Calan SR, a distributor of the RLD, as the RLD rather than Isoptin SR. Jason had to check it out to make sure that the Calan SR that was being distributed by Searle was manufactured by Knoll and was the same formulation.

As an aside even thought the initial decision has been made based upon the new BA/BE guidance to only have one RLD, i.e. the 0.3 mg tablet, for 11 strengths of a medically important drug, it may be reconsidered. Mylan was wise in doing three BE studies but you have to wonder why they did not use the same lot.

Don

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 02-Jan-2001 04:31pm EST
From: Gary Buehler
BUEHLER
Dept: HFD-600 MPN2 286
Tel No: 301-827-5845 FAX 301-594-0183

TO: Donald Hare (HARE)

CC: Robert West (WESTR)
CC: Christine Rogers (ROGERSC)

Subject: Re: levothyroxine

Don

I discussed this issue at Bio DDs and Dale suggested the same plan. Since there were no clinical trials required for this application, the feeling was that there may be some statement made that they have been marketing this same formulation for __ years etc.

[illegible] me know hat you find out.

[illegible]nks
Gary
>
>
>
>
>
>
>Gary:
>
>I called Chris Rogers, the attorney who has the lead on the
levothyroxin issue.
>She provide a lot of valuable information which may forestall the
contacting of
>JS.
>
>She suggested that I contact David Lewis, the chemist with the
responsibility
>for the 505(b) levothyroxin applications. Chris seem to think that
historical
>data was also submitted with JS NDA which may answer our question of
whether the
>Mylan ANDA used the correct formulation in their BE study.
>
[illegible]have tried calling David a couple of times but only get the answering

>machine.
>
>Stayed tuned.

E L E C T R O N I C M A I L M E S S A G E

Date: 04-Jan-2001 03:29pm EST
From: Donald Hare
HARE
Dept: HFD-604 MPN2 286
Tel No: 301-827-5845 FAX 301-594-0183

TO: Gary Buehler (BUEHLER)

CC: Robert West (WESTR)
CC: Rita Hassall (HASSALLR)
CC: Cecelia Parise (PARISEC)
CC: Dale Conner (CONNERD)
CC: Frank Holcombe (HOLCOMBE)

Subject: levothyroxin

Gary:

I met with David Lewis this afternoon and he was extremely helpful. He reviewed the JS NDA and could not find any reference to a pre-approval formulation. David then called his contact at JS with a number of questions to ask so as to be able to answer our question as to whether JS was marketing levothyroxin tablets before JS NDA was approved and if they were marketing before approval was the formulation the same as what was approved.

JS indicated that they had been marketing levothyroxin tablets for about 10 years and the approved formulation had not changed from the formulation that was marketed before approval. With this information David did not have to ask additional questions to confirm what we hope to be true i.e. Mylan had used JS approved formulation in their BE study.

Therefore based upon this JS answer to David's question any other ANDA applicant using a marketed JS levothyroxin tablet as the reference listed drug will be using the same formulation as Mylan and when approved the two ANDAs can be rated as therapeutic equivalent.

David also indicted that he would share the experience he gain in reviewing the levothyroxin NDAs with any of our chemists that are assigned to review the levothyroxin tablet ANDAs. He indicated that acceptable stability data was extremely difficult to obtain on the lower strengths.

Don

NDA 76187

Levothyroxine Sodium Tablets USP

0.025mg, 0.05mg, 0.075mg, 0.088mg, 0.1mg, 0.122mg, 0.125mg, 0.15mg, 0.175mg, 0.2mg and 0.3mg

Mylan Pharmaceuticals

Approval Date: June 5, 2002

ANDA Approval Summary

ANDA 76-187

JUL 11

Mylan Pharmaceuticals Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Levothyroxine Sodium Tablets USP, 0.025 mg, 0.05 mg, 0.075 mg, 0.088 mg, 0.112 mg, 0.125 mg, 0.15 mg, 0.175 mg, 0.1 mg, 0.2 mg and 0.3 mg

DATE OF APPLICATION: June 5, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: June 6, 2001

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Michelle Dillahunt
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA CHECKLIST FOR COMPLETENESS and ACCEPTABILITY of the APPLICATION

ANDA: 76-187 FIRM NAME: Mylan

RELATED APPLICATION(S): N/A

DRUG NAME: Levothyroxine Sodium

DOSAGE FORM: Tablets USP

FIRST GENERIC? yes

Electronic Submission (Chem) To be sent 30 days E-mail notification sent ✓

Team Leader: Mike Smela

Labeling Reviewer: angela Payne AMP

Random Assignment: RN2

Micro Reviewer: N/A

Pharmacodynamic study (Dr. Fanning): N/A

Letter Date 6/5/2001 Received Date 6/6/2001

		YES	NO
	Comments EC II ✓ On Cards ✓ Therapeutic Code 30 32 300 Thyroid	✓	
	Methods Validation Package (3 copies) ✓ (Required for Non-USP drugs)	✓	
	Archival, and Review copies ✓ Cover letter Field copy certification (original signature)	✓	
	Cover Letter ✓	✓	
	Table of Contents ✓	✓	

Sec. I	Signed and Completed Application Form (356h) (Statement regarding Rx/OTC Status)	✓	
Sec. II	Basis for Submission 7.1.10 Jerome RLD unithroid Firm Stevens Is an ANDA suitability petition required?____ If yes, consult needed for pediatric study requirement.	✓	
Sec. III	Patent Certification 1. Paragraph? IV 2. Expiration of Patent____ A. Pediatric Exclusivity Submitted?____ B. Pediatric Exclusivity Tracking System checked?____	✓	
	Exclusivity Statement ✓	✓	
Sec. IV	Comparison between Generic Drug and RLD-505(j)(2)(A) 1. Conditions of use ✓ 2. Active ingredients ✓ 3. Route of administration ✓ 4. Dosage Form ✓ 5. Strength ✓	✓	
Sec. V	Labeling 1. 4 copies of draft (each strength and container) or 12 copies of FPL ✓ 2. 1 RLD label and 1 RLD container label ✓ 3. 1 side by side labeling comparison with all differences annotated and explained ✓ 100's	✓	
Sec. VI	Bioavailability/Bioequivalence 1. Financial certification (Form FDA 3454) ✓ pg. 471 and Disclosure statement (Form 3455)____ (for BE studies only!) 2. In Vivo Study Protocol(s)____ 3. In Vivo Study(ies) ✓ 4. Computer Disk Submitted yes 1.2 orange & blue EV#10 to be sent 5. Request for Waiver of In Vivo Study(ies) ✓ 6. In Vitro Dissolution Data ✓ 7. Formulation Data Same? (Comparison of all Strengths)____ (Ophthalmics, Otics, Externals, Parenterals) 8. Paragraph IV bio study acceptable for filing NA 9. Lot numbers of products used in Bio-study RH#0747 RH#0750 10. DSI inspection request needed?____ 1st Generic____ 1st study for site____ Other RH#0708 E-mail notification to bio PMs sent____	✓ OK	

Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation ✓ See sheets attached. 2. Inactive ingredients as appropriate ✓	✓
Sec. VIII	**Raw Materials Controls** 1. Active Ingredients a. Addresses of bulk manufacturers ✓ b. Type II DMF authorization letters or synthesis ✓ c. Certificate(s) of analysis specifications and test results from drug substance manufacturer(s) ✓ d. Applicant certificate of analysis ✓ e. Testing specifications and data from drug product manufacturer(s) ✓ f. Spectra and chromatograms for reference standards and test samples ✓ g. CFN numbers ____ 2. Inactive Ingredients a. Source of inactive ingredients identified b. Testing specifications (including identification and characterization) ✓ c. Suppliers' certificates of analysis (specifications and test results) ✓ d. Applicant certificate of analysis ✓	✓
Sec. IX	**Description of Manufacturing Facility** 1. Full Address(es) of the Facility(ies) for the Manufacturing Process, Testing, and Stability Testing ✓ 2. CGMP Certification ✓ pg. 4677 3. CFN numbers 1110315	✓
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address ✓ 2. Functions ✓ 3. CGMP Certification/GLP ✓ 4. CFN numbers ____	✓
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including Microbiological Validation if Appropriate) ✓ 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with Equipment Specified ✓ 3. If sterile product: Aseptic fill ____ / Terminal sterilization ____ 4. Filter validation (if aseptic fill) ____ 5. Reprocessing Statement ____	✓

Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ✓ 2. In-process Controls a. Sampling plans and test procedures ✓ b. Specifications and data ✓ See Sheet attached		✓
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ✓ 2. Components Specification and Test Data (Type III DMF References) ✓ 3. Packaging Configuration and Sizes ✓ 4. Container/Closure Testing ✓ 5. Source of supply and supplier's address ✓		✓
Sec. XIV	**Controls for the Finished Dosage Form** 1. Sampling Plans and Test Procedures ✓ 2. Testing Specifications and Data ✓ 3. Certificate of Analysis for Finished Dosage Form ✓ Pg. 7071 →		✓
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted ✓ 2. Post Approval Commitments ✓ 3. Expiration Dating Period ✓ 4. Stability Data Submitted a. 3 month accelerated stability data ✓ b. Batch numbers on Stability records the same as the test batch R1H0747, R1H0750, R1H0708		✓
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance ✓ 2. Finished Dosage Form ✓ 3. Same lot numbers ✓		✓
Sec. XVII	**Environmental Impact Analysis Statement**		✓

Sec. XVIII	GDEA (Generic Drug Enforcement Act)/Other: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h])_____ 2. Debarment Certification (original signature) ✓✓ 3. List of Convictions statement (original signature)_____		✓

Reviewing CSO/CST Daniela T. Middleton Date 7/11/01

Recommendation: FILE REFUSE to FILE

Supervisory Concurrence/Date [signature] 11-JUL-2001

Duplicate copy sent to bio:
(Hold if RF and send when acceptable)

Duplicate copy to HFD_____ for consult

Type of consult:

Comments regarding the ANDA:

The bio studies was conducted against J Stevens Thyrox Tablets and Levo TABS. Tablets which is not the RLD. Mylan was unable to locate the Unithroid (Brand) product. See e-mail from 1/4/01 attached with a statement that Jerome Steven the did not change formulations from ~~that~~ formular used before their marketed approval.

Revised 12/99 - v:\division\revsupp\regsupp\chklst

ANDA APPROVAL SUMMARY

ANDA: 76-187

DRUG PRODUCT: Levothyroxine Sodium Tablets USP

FIRM: Mylan Pharmaceuticals Inc.

DOSAGE FORM: Tablets **STRENGTH:** 25 mcg, 50 mcg, 75 mcg, 88 mcg, 100 mcg, 112 mcg, 125 mcg, 150 mcg, 175 mcg, 200 mcg and 300 mcg

CGMP: Statement/EIR Update Status:

The EER is acceptable (OC recommendation, 8/1/01).

BIO: The bioequivalency was found to be acceptable by the Division of Bioequivalency, Office of Generic Drugs (12/31/01, Bio reviewer: H. Nguyen).

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):
Both drug substance and drug product are included in the USP. Method validation is not required.

STABILITY: (Are containers used in study identical to those in container section?)
The containers used in the stability study are identical to those described in the container section.

LABELING:

Container, carton and insert labeling have been found acceptable. (Labeling approval summary, 2/6/02)

STERILIZATION VALIDATION (IF APPLICABLE):

Sterilization validation is not required.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Executed batch sizes:

Strength	Exhibit batch
25 mcg, 50 mcg, 75 mcg	
88 mcg, 100 mcg, 112 mcg	
125 mcg, 150 mcg, 175 mcg	
200 mcg and 300 mcg	

DMF —— Levothyroxine Sodium USP drug substance
(acceptable, reviewed by Liang-Lii Huang, Ph.D. 3/12/02)

SIZE OF STABILITY BATCHES- (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

The exhibit batches were the stability batches.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME?:

Proposed production batch sizes:

Strength	Production batch size
25 mcg, 50 mcg, 75 mcg	—— tablets
88 mcg, 100 mcg, 112 mcg	—— tablets
125 mcg, 150 mcg, 175 mcg	—— tablets
200 mcg and 300 mcg	—— tablets

The manufacturing process will be the same as was used for the exhibit batch.

CHEMIST: Liang-Lii Huang, Ph.D. **DATE:** April 23, 2002
SUPERVISOR: James Fan **DATE:** April 23, 2002

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):Do you have 12 Final Printed Labels and Labeling? Yes No If no, list why:
Container Labels:
Carton Labeling:
Unit Dose Blister Label:
Unit Dose Carton Label:
Professional Package Insert Labeling:
Patient Package Insert Labeling:
Auxiliary Labeling:
Revisions needed post-approval:

BASIS OF APPROVAL:

Patent Data For NDA 21210 : No unexpired patents

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact

Exclusivity Data For NDA: No unexpired exclusivity

Code/sup	Expiration	Use Code	Description		Labeling Impact

Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Unithorid
NDA Number: 21210
NDA Drug Name: Levothyroxine sodium
NDA Firm: Jerome Stevens Pharmaceuticals
Date of Approval of NDA Insert and supplement #: S-00[illegible], app. 8/21, 2000.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
If yes, give date of labeling guidance:
Basis of Approval for the Container Labels: company used samples from Levotab and thros that are marketed by JSP since Unithroid is not commerical available.
Basis of Approval for the Carton Labeling: not applicable.
Other Comments:

REVIEW OF PROFESSIONAL LABELING CHECK LIST

	Yes	No	N/A
Established Name			
Different name than on acceptance to file letter?	X		
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23		X	
Is this name different than that used in the Orange Book?			X
If not USP, has the product name been proposed in the PF?			
Error Prevention Analysis		X	
Has the firm proposed a proprietary name? If yes, complete this subsection.			X
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			
Packaging		X	
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?			X
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		X	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?			

Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?		X	
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?			
Labeling		X	
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)	Yes	No	N/A
Labeling(continued)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR		X	
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			
Inactive Ingredients: (FTR: List page # in application where inactives are listed)		X	
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)		X	
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		X	
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?		X	
Does USP have labeling recommendations? If any, does ANDA meet them?	X		
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)		X	
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of NDA 21210/ S-001, JSP; Unithyroid, ; approved 8/21/01
2. Patent/ Exclusivities: no unexpired patents or exclusivity, firm file a paragraph PI
3. Storage Conditions:
   NDA - 20-25 C (68-77 F) with escursion between 15-30 C (59-86 F)
   ANDA - store at CRT
   USP - None
4. Dispensing Recommendations:
   NDA - none

ANDA - Dispense in a tight, light resistant container as defined in UDP. Using a child resistant closure.
USP - tight light resistant container

5. Scoring:
NDA - partial bisected.
ANDA - scored
USP - none

6. Product Line:
The innovator markets their product in bottles of 100s and 1000s
The applicant proposes to market their product in HDPE bottles of 100s with CRC.

7. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).

8. Inactive Ingredients:
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 4441-4470 section VII (Volume 10.1) .

9. Mylan, at Morgantown, will perform all operations in the manufacturing package and labeling.

Date of Review: 8/4/01 **Date of Submission: 6/5/01**

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cc: ANDA: 76-187
DUP/DIVISION FILE
HFD-613/Apayne/JGrace (no cc)
V:firmsam/mylan/lets&revs/76187na1.L
Review

/S/ 8/4/01
/S/ 8/10/2001

2

PAGE(S) HAVE BEEN REDACTED IN FULL FROM THIS DOCUMENT

Reason:

✓ b(4) Confidential Commercial Information

✓ b(4) Trade Secret Information

___ b(5) Deliberative Process; Attorney- Client and Attorney Work Product Privileges

___ b(6) Personal Privacy

___ b(7) Law Enforcement Records